

Compliance Newsletter

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General Comments

Take a break from the summer heat and look at some of the recent Warning Letters issued by the FDA. I have picked one for this issue that interprets the “21st Century” Initiative on the Regulation of Pharmaceutical Manufacturing. Such policy interpretations go beyond American borders. The EU has issued its own guidances in reflection upon this initiative, and I am sure that this WL will not go unnoticed.

For those new to the newsletter, it is built from hyperlinks. You can view the linked documents when you are on-line.

Science-Based Approach to Regulation

[FDA’s “21st Century” Initiative](#) will be a decade old in a few years, and 2 popular concepts have emerged: PAT (Process Analytical Technology); and the risk-based approach to validation. Underlying these concepts was the goal of returning to science or rather retreating from blind adherence to regulations and procedures for interpretation of the GMPs. Unfortunately, there have been few examples with established products on how to return to a science-based approach amid the flood of guidances, regulations, and procedures.

For orientation, [PAT](#) is a regulatory framework designed to “encourage the voluntary development and implementation of innovative pharmaceutical development, manufacturing, and quality assurance.” Innovative on-line measurement and control of critical parameters during manufacturing would be an example of PAT.

Lack of Science at Legacy Pharmaceuticals

The WL sent to Swiss-based [Legacy Pharmaceuticals](#) presses it to pursue a science-based approach to GMP. The focus of the inspection was the manufacturing of a topical ointment, Efudex, at its Puerto Rican facility. This pharmaceutical has a long history.

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Efudex was originally licensed in the US to Hoffmann La-Roche (Roche) in 1970. Roche sold this product to ICN Dutch Holdings in 1997. Valeant Pharmaceuticals International became the license holder and outsourced manufacturing to the Legacy plant in 2001. This is a tale involving multiple product and technology transfers. The original scientific studies supporting the license submission are probably long gone. Legacy (and Valeant) took the classical approach of freezing changes to the manufacturing process in order to remain within GMP. This process for Efudex is, after all, licensed.

The FDA concluded, "it appears that your company believes that the NDA processing approach and specifications cannot be revisited over the life-cycle of a product. For example, you emphasize in the October 18 Letter that no changes have been made to the formulation, manufacturing process, equipment or batch size since approval. Manufacturing procedures and specifications must be changed if warranted to assure product quality, however. It is essential that all issues recently raised are evaluated scientifically. You are not limited to process validation procedures established almost forty years ago for another configuration."

Further, "as a general matter, it is your responsibility under the CGMP regulations to establish appropriate specifications for your product and to continually improve your process based on information accumulated from batch manufacturing, monitoring, and testing."

It may even be true that this product hasn't changed in 40 years, but previously unrecognized quality defects must still be addressed. The authorities expect you to improve products rather than retreat behind a license, and you may need scientific studies to do that. Efudex cannot even be considered a significant risk for consumers, so that this interpretation appears to apply to any drug, including OTCs (non-prescription drugs).

Legacy was apparently diligent in recording, reporting, and investigating complaints and deviations, but never went farther than to conduct plant empirical studies. The FDA stated, "Such empirical analysis did not identify the underlying process flaws causing these problems." The WL mentioned viscosity to be a product characteristic, with poor scientific understanding, but probably critical to the quality of the product. Forty years ago, the ability to appraise the visco-elastic properties of pastes was not generally available. Now, such viscometers are commonly available, but you need to perform a scientific study to interpret the measurements and consider a control strategy. Using such viscometers for on-line control would be an example of applying PAT.

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A strange perspective on responsibilities between a license holder and a manufacturer for a drug is given by this WL. The FDA is urging Legacy to improve, i.e. change the process for manufacturing Efudex, although it is not the license holder. Valeant Pharmaceuticals would have to submit a supplement to the FDA (21CFR314.70) requesting a change to the license application, if Legacy needed to make a significant change. The data for the submission would presumably come from Legacy. Such shared responsibilities for process improvements are probably not commonly recognized and defined in these outsourcing relationships, because the process has classically been considered fixed by license.

Other Notable Warning Letters

The WL sent to medical device manufacturer [Steris Corp.](#) delineates when a design change needs to be submitted to the FDA for licensing or licensing amendments. Such changes need only have the potential to significantly affect the safety or effectiveness of the device. Here changes to controlling software, to pump specifications, and the addition of a pressure switch for the pump were all considered significant. The FDA also noted changes to: “the sterile water filter housing; lid header block; material on the PV sleeves of the pinch valve; pressure relief added to the high pressure pump; the heater element changed from copper to stainless steel; and check valve on the drain block . These changes cumulatively result in a change in the overall device design that could significantly affect safety and effectiveness.”

The WL sent to [Sandstone Medical Technologies](#) involves class II medical devices, in this case medical lasers. Besides the normal registration needed for licensing, class II devices must meet a performance standard before they can be marketed. For lasers, the standard is defined in 21CFR1040.10 and .11.

Chinese device manufacturer, [Rossmax International](#), has the dubious distinction of receiving a 2nd WL regarding the same issues. Its response to the first WL (reported in the May issue of this newsletter) prompted the second WL. Apparently, Rossmax sent a stack of SOPs to show compliance. The FDA wants to see evidence that the procedures are actually followed.

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Warning Letter Trends

Former FDA Chief Counsel Sheldon Bradshaw has publicly revealed in Congressional testimony the number of warning letters in recent years. It dropped from 1,032 in 2001 to 471 in 2007, following a 2002 policy change requiring the FDA's Office of the Chief Counsel to review such documents. The FDA argues that warning letters are only issued now for serious transgressions instead of minor ones, but the continuous downturn in WLs since 2003 would imply then that industry is getting either more compliant or smaller!

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If you have any further questions or comments, please don't hesitate to contact me directly via phone or email!